Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-26, 28-65, 67-70, 72-78, 81-95, 98-103, 105 and 110-120 are pending in the application, with 1, 15, 23, 24, 28, 117 and 119 being the independent claims. New claims 117-120 are sought to be added. The Examiner has withdrawn claims 27, 66, 71, 79-80, 96-97, 104 and 106-109 from consideration. Claims 1, 5, 24, 37, 41, 90, 91, 98, 100, 101, 103 and 114 are amended to correct typographical errors. Claims 16, 29, 88, 104, 106-109, 112 and 115 are amended to better conform to U.S. practice, *e.g.*, using conventional Markush language or making the antecedent basis more explicit. As discussed below, claims 22, 24, 25, 26, 36, 40, 47, 51, 57 and 116 are amended to more particularly point out the invention as claimed. For convenience, claims 26 and 51 are amended to explicitly describe the salts of claims 16 and 17, respectively, previously referred to by claim number. Support for these changes are found throughout the specification and claims as originally filed. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Restriction Requirement

In response to Applicants' election of Group I, the Examiner has indicated that claims 27, 66, 71, 79-80, 96-97, 104 and 106-109 are withdrawn from consideration. Applicants understand that these claims may be rejoined following allowance of a generic claim.

Objection

The Examiner has objected to claim 24 as ending in a comma and a period. The above amendment corrects this typographical error by deleting the comma.

Rejections under 35 U.S.C. § 112, ¶ 1

The Examiner has rejected claims 25-26, 47-57, 112-113 and 116 under 35 U.S.C. § 112, ¶ 1 as allegedly not being enabled. While the Examiner has acknowledged that the specification enables methods of "reducing thrombin," "treating thrombosis" and "treating deep vein thrombosis and/or pulmonary embolism," the Examiner nonetheless asserts that it does not "reasonably provide enablement for inhibiting thrombin in the treatment [or] prevention of diseases or preventing thrombosis, cardiovascular event, venous thromboembolic event, thromboembolic events or arterial diseases." Applicants respectfully disagree with these assertions and traverse the rejection.

The Examiner cites *The American Heritage Dictionary* for the definition of "prevent" as "to keep from happening; to keep from doing something," and asserts that "[t]he interpretation of the instant claims allows for the prevention, cure, eradication or total elimination of thrombosis or any diseases or conditions associated with thrombosis by the administration of said compounds." Office Action, at page 3. Building upon this definition, the Examiner states that "[t]here are no known compounds of similar structure which have been demonstrated to prevent thrombosis or treatment of any disease or condition related to thrombosis", that "this assertion is contrary to what is known in medicine" and that "[t]he existence of such a 'magic bullet' is contrary to our present

understanding of pharmacology." Office Action, at pages 3-4. Applicants respectfully disagree.

First, Applicants note the Examiner's acknowledgement of novelty and non-obviousness of the claimed invention ("[t]here are no known compounds of similar structure which have been demonstrated to prevent thrombosis or treatment of any disease or condition related to thrombosis"). However, the Examiner's use of a general purpose dictionary to construe the terms of the pending method claims is at odds with the Federal Circuit's directive in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005).

A claim term is generally given its ordinary and customary meaning, *i.e.*, the meaning that the term would have to a *person of ordinary skill in the art* as of the effective filing date of the application. *Phillips*, 415 F.3d at 1312-13. The person of ordinary skill in the art is deemed to read the claim term in the context of the entire patent, including the specification. *Id.* at 1313. The present specification indicates that the compounds of the invention as presently claimed are thrombin inhibitors, and therefore indicated in the therapeutic and/or prophylactic treatment of various thrombosis-related disorders. *Specification*, at page 36, line 12 through page 38, line 10 (¶¶ [0286-0303] in the specification published as US 2004/0138175 A1). The claims are thus to be read in the context of compounds indicated for treatment and prevention of thrombosis-related disorders.

The concept of prevention or prophylaxis of a disorder, as understood in this context by a *person of ordinary skill in the art*, does not pertain to a "magic bullet" or to the "cure, eradication or total elimination" of a disorder, as shown by, for example, contemporaneous usage in J.A. Heit, *CHEST*, **2003**, *124*, 40S-48S ("*Heit*"):

> Venous thromboembolism (VTE) is a common and potentially lethal disease that recurs frequently and is associated with long-term impairment and suffering. . . . Universal effective prophylaxis of hospitalized patients would significantly reduce the incidence of VTE. Parenteral direct thrombin inhibitors are safe and effective for both prevention and treatment of acute VTE . . . .

Heit, at 40S, abstract. Thus, in one sense, a person of ordinary skill in the art understands prevention or prophylaxis of a disorder to mean "reducing the incidence of" the disorder. Similarly, W.H. Geerts *et al.*, *CHEST*, **2001**, *119*, 132S-175S ("*Geerts*") states:

> In the summary tables, the rates of deep vein thrombosis have been pooled from the eligible trials for each intervention and then compared with the rate among pooled, untreated or placebo-treated control patients to determine the reduction in relative risk. Because comparisons among the interventions are indirect, the results of this pooling analysis provide an approximate guide to the relative efficacy of various prophylactic strategies.

Geerts, at 132S, left-hand column. Thus, in another sense, a person of ordinary skill in the art understands prevention or prophylaxis of a disorder to mean reduction in risk of affliction by the disorder. Importantly, T.M. Hyers *et al.*, *CHEST*, **2001**, *119*, 176S-193S ("*Hyers*") recites:

> All antithrombotic therapy with either anticoagulants or platelet-active drugs is prophylactic, since these agents interrupt progression of the thrombotic process . . . .

Hyers, at 176S, left-hand column. Thus, in yet another sense, a person of ordinary skill in the art understands a treatment that interferes with the progression of a process that leads to a disorder, to be prevention or prophylaxis of that disorder. In accordance with *Phillips*, it is the contemporaneous understanding of a person of ordinary skill in the art such as that provided above, rather than non-contextual definitions from a general purpose dictionary, that governs claim construction.

The Examiner has acknowledged that the present method claims are enabled for, *inter alia*, treating thrombosis. As indicated in both *Heit* and *Hyers*, the skilled artisan would understand that the direct thrombin inhibitors of the claimed invention would therefore be useful for both treating and preventing thrombosis. This is because, as noted in *Hyers*, thrombin inhibitors act by hindering thrombosis, and are thus prophylactic by nature. Thus, Applicants respectfully submit that the present method claims are enabled for treating and/or preventing thrombosis.

Furthermore, inasmuch as the present claims directed to treating and/or preventing thrombosis are enabled, Applicants respectfully submit that the narrower claims directed to treating and/or preventing various disorders that arise as a result of thrombosis are similarly enabled. It is evident to the skilled artisan that hindering the process which gives rise to a disorder will necessarily aid in the treatment and/or prevention of the disorder. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, ¶ 1.

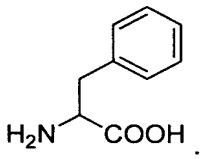
Rejections under 35 U.S.C. § 112, ¶ 2

The Examiner has rejected claims 16 and 24 under 35 U.S.C. § 112, ¶ 2 as allegedly indefinite. Applicants respectfully traverse.

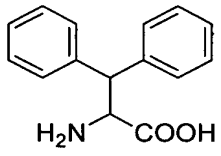
Regarding claim 16, the Examiner asserts that one of ordinary skill in the art would not understand the meaning of "wholly or partially hydrogenated analogues thereof." Applicants respectfully disagree.

Claim 16, as amended, recites, "The formulation of claim 15 wherein aa^1 is selected from Phe, Dpa and wholly or partially hydrogenated analogues thereof." Thus, the wholly or partially hydrogenated analogues referred to are of Phe and/or Dpa. The

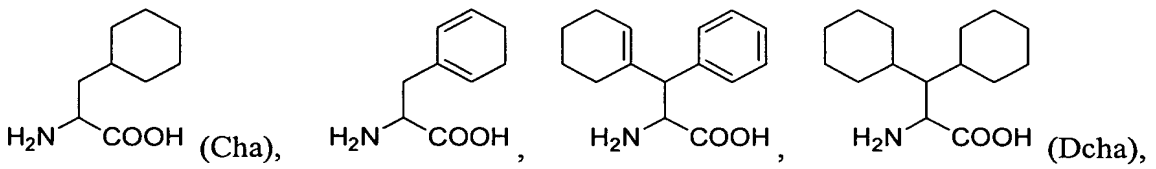
specification defines Phe as phenylalanine, and Dpa as diphenylalanine. *Specification*, at page 21, lines 8 and 39 (¶¶ [0145] and [0170]). One of ordinary skill in the art would know the structure of the naturally occurring amino acid phenylalanine:



The structure of diphenylalanine, from its name, is similarly clear:



The concept of hydrogenation, *i.e.*, the addition of H_2 to a molecule, is fundamental in organic chemistry. *See, e.g.*, G.M. Loudon, *Organic Chemistry*, 3d ed., Benjamin/Cummings Publishing Co.: Redwood City, CA (1995) ("*Loudon*"), pp. 161-62. Even introductory organic chemistry texts discuss hydrogenation of benzene rings, such as those contained in Phe and Dpa. *See, e.g., Loudon* at 775-76. Applicants respectfully submit that one of ordinary skill in the art would understand the phrase "wholly or partially hydrogenated analogues" of Phe or Dpa to refer to compounds having a structure that would result from the nominal addition of one or more equivalents of H_2 to Phe or Dpa, such as



and the like. *See Loudon* at 776. The specification confirms this when it states that "[t]he wholly hydrogenated analogues are Cha and Dcha." *Specification*, at page 26,

lines 31-32 (¶ [0217]). Cha and Dcha are defined as cyclohexylalanine and dicyclohexylalanine, respectively. *Specification*, at page 21, lines 35 and 38 (¶¶ [0167] and [0169]). Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 16 under 35 U.S.C. § 112, ¶ 2.

Regarding claim 24, the Examiner asserts that the term "a pKb of about 7 or more" is indefinite because no upper limit of pKb is recited in the claim. Applicants respectfully disagree.

The concept of equilibrium constants of bases expressed as K_b or pK_b is well known to a person of ordinary skill in the art. *See, e.g.*, S.S. Zumdahl and S.A. Zumdahl, *Chemistry*, 5th ed., Houghton Mifflin Company: Boston (2000) ("*Zumdahl*"), at 658-85. Namely, for the reaction between a base, B, and water, represented by the equation

$$B_{(aq)} + H_2O_{(l)} \leftrightarrows BH^+_{(aq)} + OH^-_{(aq)}$$

$K_b = [BH^+][OH^-]/[B]$, and $pK_b = -\log K_b$. *Zumdahl*, at 667, 685. The constants K_b and pK_b for a given base are a measure of the *relative* strength of that base, and the relevant comparison is between the K_b's or pK_b's of two different bases. *Zumdahl*, at 662, 685. The difference between the values indicates which base is stronger and by what degree. *Id.* The skilled artisan further knows, in accordance with the equation above, that the upper and lower limits of K_b and pK_b for a given base are governed by the solvent in which the base is dissolved, namely, water. Thus, while the Examiner asserts that the term "a pK_b of about 7 or more" refers to *any* value greater than about 7, and therefore "leaves the reader in doubt as to the meaning of the invention," the skilled artisan understands that there are practical upper and lower limits to the quantity, imposed by the solvent, and that not knowing the exact value of the upper limit in no way renders the

invention "vague and unclear," or otherwise prevents the skilled artisan from determining whether or not he is infringing the claim. The claim as previously presented simply required that the easily-measured pK_b of the base in question be compared to the value recited in the claim, "about 7 or more."

Notwithstanding Applicants' belief that claim 24 as previously presented was fully compliant with 35 U.S.C. § 112, ¶ 2, the above Amendment deletes the phrase, "basic organic nitrogen containing compounds having a pKb of about 7 or more," and replaces it with the phrase, "strongly basic organic nitrogen containing compounds." Support for this amendment is found in the specification, *inter alia*, at page 22, lines 12-13 (¶ [0180]), which explains that a "strong base" is one capable of reacting with a boronic acid ("Strong base=a base having a sufficiently high pKb to react with a boronic acid. Suitably such bases have a pKb of 7 or more, e.g., 7.5 or more, for example about 8 or more"). Applicants respectfully submit that claim 24 as amended is also fully compliant with 35 U.S.C. § 112, ¶ 2, and respectfully request reconsideration and withdrawal of the rejection of claim 24 under this section.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 1-26, 28-65, 67-70, 72-78, 81-95, 98-103, 105 and 110-116 under 35 U.S.C. § 103(a) as allegedly obvious over Claeson (*Biochem J.*, 1993) in view of Skordalakes (*J. Am. Chem. Soc.*, 1997), and further in view of Ketner (WO 94/21668), Wienand (WO 97/05161) and /or Shoichet (WO 00/35904). Applicants respectfully traverse.

Briefly, the Examiner asserts (1) that Claeson teaches an organoboronic acid pinanediol ester inhibitor of thrombin having a neutral thrombin S1-binding moiety

linked to a hydrophobic thrombin S2/S3-binding moiety; (2) that Skordalakes teaches that the removal of pinacol ester would not alter the analogous thrombin-inhibiting activity of the organoboronic acid; (3) that Ketner demonstrates the "routine knowledge" in removing pinacol ester protecting groups by transesterification to make the boronic ester; (4) that Wienand demonstrates the "routine knowledge" in preparing boronic acid derivatives of formula (I) into various pharmaceutical dosage forms and salt forms; and (5) that Shoichet demonstrates the "routine knowledge" in preparing boronic acid derivatives in various salt forms.

To establish a *prima facie* case of obviousness, the prior art must teach or suggest each and every element of the claimed invention. Additionally, there must be some suggestion or motivation, either in the prior art itself or in the knowledge generally available to one of ordinary skill in the art, to modify the prior art or combine the teachings of the prior art in the matter posited by the Examiner. *See, e.g.*, *In re Kahn*, 441 F.3d 977, 987-88 (Fed. Cir. 2006); *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000).

> However, a reference that teaches away from a given combination may negate a motivation to modify the prior art to meet the claimed invention. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant."

Ormco Corp. v. Align Technology, Inc., 05-1426, Slip op. at 13 (Fed. Cir. Aug. 30, 2006) (quoting *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)).

The Examiner asserts that one of ordinary skill in the art would expect that removing the pinacol ester from the compound allegedly disclosed in Claeson would produce a compound with analogous properties. The Examiner further asserts that

preparation of boronic acid derivatives into pareneteral dosage forms is well within the skill of the artisan. Applicants respectfully submit that one of ordinary skill in the art would have had no motivation to make a parenteral dosage form of a salt of a boronic acid. In fact, the person of ordinary skill in the art would have been *taught away* from making such a dosage form.

Boronic acids are known to be unstable. For example, Intl. Patent Appl. Publ. No. WO 02/059130 ("*Gupta*") teaches that alkylboronic acids are relatively difficult to obtain in analytically pure form, that they readily form boroxines (anhydrides) under dehydrating conditions, and that they are often air-sensitive, *e.g.*, to oxidation; and concludes that "[t]hese difficulties limit the pharmaceutical utility of boronic acid compounds." *Gupta*, at ¶ [0004]. Similarly, S. Wu *et al.*, *J. Pharm. Sci.*, **2000**, *89*, 758-65 ("*Wu*") reports, "The chemical stability of peptide boronic acid derivatives, from a formulation perspective, has not been extensively reported in the literature to our knowledge. During an effort to formulate 2-Pyz-(CO)-Phe-Leu-$B(OH)_2$ for parenteral administration, the compound showed erratic stability behavior and was quite unstable in certain solvents." *Wu*, at 758, right-hand column. *See also Specification*, at page 4, lines 24-27; page 4, line 35 through page 5, line 2; and page 5, lines 4-7 (¶¶ [0035], [0037-0038]).

Aware of the instability of boronic acids and of the "erratic stability behavior" of a peptide boronic acid during attempts to formulate it for parenteral administration, a person of ordinary skill, upon reading the references, would be led in a direction "divergent from the path that was taken by the Applicants." Recognizing the "need in the art for improved formulations of boronic acid compounds", *Gupta* reports that

"lyophilization of an aqueous mixture comprising a boronic compound and a compound having at least two hydroxyl groups produces a stable composition that readily releases the boronic acid compound upon dissolution in aqueous media." *Gupta*, at ¶ [0005]. In other words, *Gupta* teaches solving the stability problem by formulating the boronic acid as a lyophilizate with another compound, *e.g.*, a sugar, which lyophilizate can be reconstituted with an aqueous solvent such as saline for administration (which a person of ordinary skill in the art would recognize as suitable for parenteral rather than oral administration). *Gupta*, at ¶¶ [0136], [0144]. *See also Specification*, at page 5, lines 4-18 (¶¶ [0038-0046]).

In a similar vein, V. Martichonok and J.B. Jones, *J. Am. Chem. Soc.*, **1996**, *118*, 950-58 ("*Martichonok*") teaches formation of the corresponding diethanolamine ester to impart stability to boronic acids. *Martichonok*, at 951, right-hand column ("this derivatization also provided protection against possible autoxidation of the acetamido boronic acids [] by atmospheric oxygen"). D.S. Matteson *et al.*, U.S. Patent No. 5,681,978 ("*Matteson*") similarly teaches oxidative resistance of the pinacol ester of a boronic acid. *Matteson*, at column 4, lines 57-67. *See also Specification*, at page 4, lines 29-33 (¶ [0036]).

Thus, aware of both the problem with stability of boronic acids, particularly in parenteral formulations, and two reported solutions to the problem, a person of ordinary skill in the art would not have been motivated to make the claimed invention but rather would have pursued one of the aforementioned solutions. For at least this reason, the cited references do not render any of claims 1-26, 28-65, 67-70, 72-78, 81-95, 98-103,

105 or 110-116 *prima facie* obvious. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Double Patenting

The Examiner has provisionally rejected claims 1-24, 28-29, 40-46, 58-65, 67-70, 72-78, 81-95, 98-103, 105, 110, 114 and 115 for non-statutory obviousness-type double patenting over claims 19-23 and 28-36 of Application No. 10/937,181 or claims 1-24 and 55-58 of Application No. 10/937,854. Additionally, the Examiner has provisionally rejected claims 1-26, 28-65, 67-70, 72-78, 81-95, 98-103, 105, 110-116 for non-statutory obviousness-type double patenting over claims 1-38 of Application No. 10/659,179, which has issued as U.S. Patent No. 7,112,572, or Application No. 10/659,178.

Regarding the rejections over U.S. Patent No. 7,112,572 and Application No. 10/659,178, Applicants respectfully request that these rejections be held in abeyance until the Examiner has identified allowable subject matter. At such time, Applicants will consider filing a terminal disclaimer.

Furthermore, Applicants respectfully request withdrawal of the rejections over Application Nos. 10/937,181 and 10/937,854, each filed September 8, 2004, nearly one year after the filing date of the present application. It is believed that the present Amendment and Reply places the application in condition for allowance. Thus, in accordance with MPEP § 804, it is proper for the Examiner to withdraw the provisional obviousness-type double patenting rejections from the present application and require a terminal disclaimer in the later-filed applications.

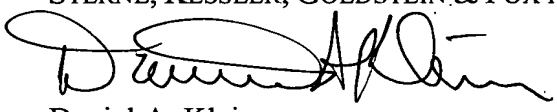
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Daniel A. Klein
Attorney for Applicants
Registration No. 54,225

Date: October 25, 2006

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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